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Creatine

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Synonyms

(α-Methylguanido)acetic acid; 2-(carbamimidoyl-methyl-amino)acetic acid; Methyl glycocyamine; Methylguanidoacetic acid; N-(aminoiminomethyl)-N-methyl-glycine; N-amidinosarcosine; N-guanyl-N-methylglycine; N-methyl-N-guanylglycine

Definition

Creatine is a nonessential dietary element found in high abundance in meat and fish. Because of its molecular structure, creatine is a member of the ► guanidino acid family. It is not an amino acid! Normal daily intake of creatine from an omnivorous diet approximates 1 g [1]. However, creatine is also synthesized within the body, primarily in the liver, from two amino acids by a two-step reaction at a rate of about 1 g per day. In the first step catalyzed by arginine:glycine amidinotransferase, guanidinoacetate is formed from arginine and glycine. In the second step, a methyl group of S-adenosylmethionine is transferred to guanidinoacetate and creatine is formed.

Approximately 120 g of creatine is found in a 70-kg male, 95% in skeletal muscle. Total creatine exists as both free creatine and phosphorylcreatine. The highest levels of creatine and phosphorylcreatine are found in skeletal muscle, heart, spermatozoa, and photoreceptors cells of the retina. Intermediate levels are found in brain, brown adipose tissue, intestine, endothelial cells, and macrophages, and low levels are found in lung, spleen, kidney, liver, white adipose tissue, blood cells, and serum.

Creatine is an important source of chemical energy for muscle contraction because it can undergo phosphorylation with the formation of phosphorylcreatine, and reversible, with donation of the phosphate group to ADP to form ATP. This reaction is catalyzed by the enzyme ► creatine kinase and is a rapid source of high-energy phosphate for high-intensity, short-duration physical activity. The initial idea for creatine supplementation in athletes was improving the energy storage under the form of intramuscular phosphorylcreatine.

Creatine kinase activity is higher in skeletal muscle than in others tissues. Evidence exists that the role of the creatine/phosphorylcreatine shuttle system also plays an essential role in energy homeostasis in the heart, brain, and retina to ensure proper development and function.

Mechanism of Action

Since the paper of Roger Harris and collaborators in 1992 who reported for the first time beneficial effects of creatine supplementation, creatine has become one of the most popular dietary supplements in the world. Synthetic supplements exist as creatine monohydrate or various creatine salts, such as creatine citrate or creatine pyruvate, the latter being more soluble than creatine monohydrate.

Muscle creatine content averages 110–120 mmol/kg dry mass and can be increased up to 130–160 mmol/kg dry mass after creatine supplementation, which represents an increase of about 15–30%. Two strategies of supplementation exist. In most conditions, 20 g of creatine is ingested every day for 5 days; thereafter, 3–5 g is consumed daily to maintain muscle uptake. A second strategy omits the loading phase. In this case, the rise in muscle creatine content is slower, but reaches the same level after about 15 days.

To date, several hundred studies have been conducted to evaluate the efficacy of creatine supplementation for improving exercise performance. Nearly 70% of these studies have reported a significant improvement in exercise capacity. The gain in performance can reach up to 10% or 15% depending on the variable of interest, on the exercise mode, and on the exercise intensity. Typically, creatine supplementation seems to be effective in high-intensity, short-duration exercise wherein phosphorylcreatine availability is a limiting factor and not in other situations like in endurance events.

Most, if not all, commercial and anecdotal claims of the beneficial effects of creatine supplementation are focused on the increase in muscle strength and muscle

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protein mass. Several scientific publications have also emphasized the increase in strength and the higher muscle protein content associated with the increase in body mass or fat-free mass. The pertinent question for researchers and practitioners is whether there is sufficient experimental evidence to support these allegations and what are the mechanisms behind.

After a few weeks of creatine supplementation, the average increase in body mass reported in the literature amounts to 1–2 kg, or 1–2.3% of total body mass, although about 30% of published articles do not report any change. In well-controlled laboratory conditions, creatine supplementation has been shown to improve muscle strength by about 5–20%.

Several hypotheses have been proposed to explain these effects on lean body mass and muscle strength. Creatine per se could induce muscle hypertrophy due to water retention since cellular water content may influence protein metabolism. Creatine has been shown to increase total body water including intracellular water. However, the relative volume of the body water compartments remains unchanged after creatine supplementation. Therefore the gain in body mass cannot be attributed to water retention alone but to an increase in dry matter accompanied by a normal water volume.

Evidence accumulated over the past 15 years suggests that the primary mechanism by which creatine exerts its ► anabolic effect in healthy subjects who are weight training is by allowing them to work at a higher proportion of their maximal voluntary contraction force and thus increase the training stimulus. However, this mechanism may not explain all the observations like the higher force production observed in patients suffering from myopathy (see below).

The increase in lean body mass after creatine supplementation could be the result of a larger protein synthesis or a decrease in protein breakdown or both together. However, it has been reported that creatine had no effect on skeletal muscle protein synthesis and breakdown, whether at rest or after resistance exercise suggesting that short-term creatine loading does not have a significant effect on measures of skeletal muscle protein balance.

Other experiments conducted on a longer period of time reported that creatine supplementation resulted in larger increases in type I, IIA, IIAB muscle fiber cross-sectional area compared with placebo after 12 weeks of heavy resistance training and after 2 weeks of leg immobilization followed by 10 weeks of rehabilitation. Creatine supplementation also leads to greater increases in type I and II MHC (myosin heavy chain) mRNA abundance and protein content after 12 weeks of resistance training, suggesting that an increase in MHC synthesis may account in part for the greater increase in muscle size with creatine supplementation. Creatine supplementation has also been shown to amplify the increase in ► satellite cell number and myonuclei concentration in human skeletal muscle fibers during 4–16 weeks of resistance training.

In vitro experiments were conducted with the goal of understanding the molecular mechanisms by which creatine stimulates muscle growth. The results indicated that Akt/PKB and p38 MAPK and their downstream targets play essential roles in the enhancement of ► myotubes differentiation by creatine [2]. But, the question remains as to how creatine activates the Akt/PKB and the p38 MAPK pathways.

There is a close functional coupling between the ► sarcoplasmic calcium ATPase and the creatine kinase system. This functional coupling may explain the faster skeletal muscle relaxation time observed after creatine loading in humans, and the impairment in skeletal muscle excitation/contraction in a mouse model lacking cytosolic and mitochondrial creatine kinase. The increase in calcium uptake may explain the reduction in cytosolic calcium accumulation and enhanced survival of muscular dystrophic myotubes incubated with creatine.

Clinical Use

Creatine supplementation has become one of the most popular ergogenic aids among athletes for enhancing acute performance or training adaptations. In a clinical perspective, the potential exists for creatine to be a therapeutic replacement strategy in neurological and/or muscular diseases as the concentration of phosphorylcreatine in resting skeletal muscle is lower in patients with muscular dystrophy/congenital myopathies, inflammatory myopathies, Huntington's disease, Friedrich's ataxia, and mitochondrial cytopathies, and with normal aging. Brain phosphorylcreatine concentration is lower in patients with mitochondrial cytopathy, cerebral ischemia, and bipolar affective disorders. Creatine supplementation of those patients may result in a partial restoration of intracellular creatine concentration, an increase in type II muscle fiber diameter, improved exercise capacity, increased muscle strength, reduced headache frequency, normalization of electrocardiogram abnormalities, etc., depending on the type and the severity of the disorder.

Diagnostics

Whereas the determination of the ► isoenzymes of creatine kinase or phosphorylcreatine kinase in plasma has been extensively studied and used in the diagnosis of acute myocardial infarction, this paragraph will be focused on the use of creatine itself and its precursors in creatine

deficiency syndromes [3] and in neuromuscular diseases [4]. Creatine deficiency syndromes represent a group of inborn errors of creatine synthesis (arginine:glycine amidinotransferase deficiency and guanidinoacetate methyltransferase deficiency) and transport (creatine transporter deficiency). All three defects can be diagnosed by in vivo nuclear magnetic resonance spectroscopy of the brain, which shows a severe reduction or absence of creatine. Laboratory investigations for the diagnosis start with the analysis of guanidinoacetate, creatine, and creatinine in plasma and urine. Measurement of guanidinoacetate, creatine concentrations, and calculation of creatine/creatinine and guanidinoacetate/creatinine ratios in urine makes possible the identification of arginine:glycine amidinotransferase (low creatine with low guanidinoacetate excretion) and guanidinoacetate methyltransferase deficiencies (low creatine with high guanidinoacetate excretion), as well as creatine transporter defects (high creatine/creatinine and guanidinoacetate/creatinine ratios in urine). Moreover, enzyme assays for arginine:glycine amidinotransferase or guanidinoacetate methyltransferase, or a creatine uptake assay for the transporter defect can be performed. DNA mutation analysis of the genes involved can prove the defects at the molecular level. To diagnose patients with creatine transporter deficiency, mutation analysis may be the only choice.

People with neuromuscular disorders such as mitochondrial cytopathies, Huntington's disease, inflammatory myopathies, and Duchenne dystrophy can have lower skeletal muscle total creatine and phosphocreatine concentrations than control subjects. This may be due to lower creatine transporter content or an impairment of energy charge, a measure of the relative amounts of adenosine tri-, di-, and monophosphate in the cell, in these patients. Creatine, phosphocreatine, and adenosine tri-, di-, and monophosphate can be determined in muscle biopsies by biochemical analyses or by nuclear magnetic resonance spectroscopy.

It is of note that guanidinoacetate methyltransferase and arginine:glycine amidinotransferase deficiencies and some neuromuscular disorders are treatable by, or at least benefit from, oral creatine supplementation, but patients with creatine transporter deficiency do not respond to this type of treatment.

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